We propose an alternative modeling framework that drastically reduces the number of parameters by integrating discrete subcellular processes into a framework of weakly coupled functional modules. Module interaction is governed by few rules. In the case of cell spreading, we model the stochastic formation of FXs by discrete modules representing lamellipodial and filopodial activity, and consider the spatiotemporal interactions of these modules. These interactions are regulated by the top-level cellular objective. More specifically, maturation of nascent FXs and accompanying stress-fibers recruitment is driven by actin bundle bridging of overly-large distances between consecutive adhesions and the eventual spatial incorporation of stable filopodia by the lamellipodia. Based on this framework, an iterative and non-deterministic numerical algorithm was developed that enabled prediction of spread cell morphology (focal adhesion and stress-fiber layout), in a time dependent manner. Numerical outcomes were compared to a wide range of experimental evidence. For all tested substrates, the model provided robust replication of the experimental analog. We interpret this fact to imply that the selected functional modules and governing top-levels rules for their interaction were adequate to describe cell spreading.

3311-Pos Board B416
Developing a Fast Polarizable Force Field for Biophysical Simulations
George Kaminski.
Computer simulations have become very helpful in biophysical studies. It has been demonstrated by our and other groups that explicit treatment of the electrostatic polarization is crucial for obtaining biochemically accurate computational data in a variety of cases. For example, we have managed to calculate pKa values for protein residues within 0.6 - 0.7 pH units of the available experimental data. We have also shown that some experimentally known protein-ligand complexes have to be modeled with explicit polarization in order to reproduce the very existence of the complexes. Our results also allow to conclude that simulation of complexes with the Cu+ ion can have a ca. three-fold error in the magnitudes of the binding energies if the polarization is not included. We are now developing a complete polarizable force field for proteins using the second-order approximation formalism which permits to increase the computational speed by ca. an order of magnitude. Results of this ongoing development will be presented, and a number of relevant issues (including the relative importance of quantum mechanical and experimental data in fitting of torsional parameters) will be discussed.

3312-Pos Board B417
Compartmental Analysis of Intravaginal HIV Transport and Neutralization by Microbicides
David F. Katz, Jason A. Chen.
Microbicides are topically acting molecules intended to inhibit HIV-transmission by acting within luminal fluids and/or vaginal mucosa. Gels are a promising microbicide delivery modality, with clinical evidence that they can reduce the rate of sexually-transmitted HIV in women (Karim et al, 2010). We created a model of interacting vaginal co-transport of HIV virions and gel-introduced microbicides in four compartments: semen, gel, vaginal fluid, mucosa. Imaging studies of gel distribution have shown that mucosal surfaces has incomplete gel coating; there can be substantial surface area directly exposed to semen. HIV and microbicide transport occur by diffusion and convection, the latter modeled using Taylor dispersion theory. Here, the active microbicide is an HIV entry inhibitor that must collide with virions in sufficient numbers before they arrive at the mucosal surface to prevent transmission. Key model output is the time-dependent number of non-neutralized virions arriving at the tissue surface. Key inputs are: fraction of surface with coating; coating thickness distribution; viral load in semen; microbicide concentration in gel; parameters of HIV neutralization mechanism; HIV and microbicide diffusion coefficients in gel, semen and vaginal fluid; and time interval between gel application and semen deposition. Results show that infectious HIV transport to tissue is largely over uncoated regions, since HIV diffusion in gel is significantly restricted (Lai et al, 2010). If fractional coated area >90%, most reasonable combinations of system parameters cause substantial HIV neutralization, with small numbers (~ 1000) of still-infectious virions reaching tissue. Lower fractional coated areas and increased HIV diffusion coefficients result in increased flux of infectious virions to tissue in a multivariate manner delineated by the model. This modeling helps improve our understanding of how HIV transmission can be reduced by rationally designed microbicides. [Support: NIH AI077289 and Duke CFAR].

3313-Pos Board B418
Deriving Effective Force and Moment due to Pairwise Interactions in Coarse Grain Simulations
Mohammad Poursina, Kurt S. Anderson, Jeremy Laflin.
We extend the approach used to approximate the long range gravitational force and the associated moments in spacecraft dynamics to calculate the pairwise forces in coarse grain simulations. First, we provide a relatively accurate approximation of the resultant force applied from an atom $\boldsymbol{P}$ to a rigidified superatom. Since this resultant force does not generally act through the center of mass of the superatom, it creates a moment about the center of mass of the body. This potentially valuable moment is completely neglected in bead model representations. We also calculate this moment which is very useful when the equations of motion are formed in articulated multibody-based framework. In this process, assuming each superatom as a discontinuous rigid body, we introduce the concept of the pseudointertia dyadic $\boldsymbol{I}_{\alpha}$. If the governing force field is the gravitational force, this pseudoinertia tensor represents the inertia matrix of the rigid body or system of particles. We show that the resultant force and moment applied to the superatom only depend on the location of the center of mass of the superatom with respect to the atom $\boldsymbol{P}$, and the pseudointertia tensor of the body. This tensor is calculated for each rigid domain of the system before starting the simulation; therefore, there is no cost associated with this tensor during the course of the simulation. Then, based on the results obtained in the previous step, we calculate the resultant force and moments between two rigid pseudoatoms due to the pairwise interactions among the individual atoms belonging to one superatom and the other one. We show that the resultant force and moments are functions of the relative location of the centers of mass of the bodies, and the pseudoinertia dyadic of the individual pseudoatoms.

3314-Pos Board B419
Relationship of the 2′-Hydroxyl Orientation in RNA to Watson-Crick Base Pair Opening
Elizabeth Denning, U. Deva Priyakumar, Alexander D. MacKerell Jr.
RNA molecules are one of the more versatile macromolecules within a cell as they have a variety of structures and functions. Thus, it is important when studying RNA using empirical force fields, to consider the models and methodologies used to study RNA, including the quality of force field parameters. CHARMM27 force field parameters exhibits Watson-Crick (WC) basepair opening in RNA molecules. Here, we present a series of new RNA force field parameters that improve the behavior of RNA molecules. The updates result in changes in the distribution of the 2'-hydroxyl torsion leading to a reduction the frequency and extent of WC base-opening events. As a result of the shift in the 2′-hydroxyl distribution, we observe results that are in improved agreement with experimental and RNA survey data. The optimal force field parameter was applied to study the behavior and folding mechanisms of different types of RNA molecules.

3315-Pos Board B420
Development of the Charmm Polarizable Force Field for Polypeptides Based on Drude Oscillators
Pedro E.M. Lopes, Xiao Zhu, Albert Lau, Benoit Roux, Alexander D. MacKerell Jr.*.
Ongoing developments of polarizable CHARMM force field for proteins, based on the classical Drude oscillator, are presented. Inclusion of polarizability has the potential to describe physical properties of complex systems in a way not possible with current additive force fields. However, polarizable force fields are extremely sensitive to the environment and extreme care has to to be used in their development. For example, small changes of the electrostatic parameters result in large variations of the calculated properties relative to the reference QM values. In this work we describe the steps in optimization of the force field. The bonded parameters were developed based on the reproduction of QM and crystal structures and vibrational spectra of small models (ex. NMA, alanine dipeptide and proline dipeptide). Determination of the crucial electrostatic parameters was based on reproduction of QM electrostatic properties, dipole and quadrupole moments, of small (NMA and alanine dipeptide) and larger models (alanine 5-mer polypeptide) in different conformations. Determination of the electrostactic parameters pose a considerable challenge since ultimately, they have to be able to describe the electrostatic properties of small and extended compounds (ex. polypeptides) alike. VdW parameters were developed following the customary reproduction of condensed phase results (heats of vaporization and free energies of hydration). Finally, adjustments needed to fine tune the agreement between calculated and target properties of larger polypeptides are described.

3316-Pos Board B421
No New Islet Formation after Neonatal Islet Fission
Junghyo Jo, German Kilimnik, Abraham Kim, Manami Hara, Vipul Periwal.
Glucose homeostasis is regulated by the islets of Langerhans, a cluster of micro-organs embedded in the exocrine pancreas. These pancreatic islets range in size from a few to several thousand endocrine cells independent of species over a range of body sizes, suggesting an optimal functional size. Humans have more but not larger islets than mice. To examine the developmental processes that produce this size range of islets, we used a novel method that images all the islets in an intact pancreas of the transgenic mice expressing a fluorescent protein specifically in beta cells. Based on changes of the islet size distribution from postnatal day 1 to week 20, we analyzed islet developmental processes such as birth, growth and fission with mathematical modeling. No new islets were formed after postnatal week 3. At early postnatal days, islet growth was size-dependent with more active cell

proliferation in smaller islets than in larger islets. In adulthood, however, every beta cell in an islet of arbitrary size ultimately has an equally small proliferation potential. In addition to this limited islet growth, fission of large islets occurred most actively at postnatal week 3, and contributed to maintaining a limited range of islet sizes. On the other hand, in a tumor (insulinoma) progression model, we found unlimited islet growth, with especially accelerated cell proliferation in larger islets. We conclude that islet size is constrained by preferential growth of small islets and fission of large islets in the early postnatal period, and a low rate of proliferation in maturity.

3317-Pos Board B422

In Silico Titration of Biomolecules: Explicit Solvent Constant pH Molecular Dynamics

Serena Donnini, Florian Tegeler, Gerrit Groenhof, Helmut Grubmüller.

The pH is an important parameter in macromolecular systems as it determines the protonation state of ionizable groups and consequently influences the structure, dynamics and function of molecules in solution. In most force field simulation protocols, however, the protonation state of a system (rather than its pH) is kept fix and cannot adapt to changes of the local environment. Here, we present a method to perform molecular dynamics simulations in explicit solvent at constant pH. During the simulation the protonation states of titratable groups are allowed to change dynamically, and the titration curves agree with experiment. Our method is based on the lambda-dynamics approach, in which the dynamics of the titration coordinate lambda is driven by generalized forces between the protonated and deprotonated states. Constant pH simulations can be achieved by accounting for the pH dependence of the hydration free energy. As a benchmark, titration curves of amino acid analogues and a di-peptide, as well as of turkey ovomucoid inhibitor protein were calculated.

3318-Pos Board B423

Estimating the Orientational Entropy of Water at Protein Interfaces

Stephanus M. Fengler, Helmut Grubmüller.

The entropy of solvents significantly contributes to the stability of the native state of proteins. However, obtaining solvent entropies from molecular dynamics simulations remains a computational challenge. Reasons for this are first, that the phase space of solvent molecules poorly converges because they sample a shallow free energy basin. Second, its dimensionality rapidly grows with the number of molecules.

To address the problem of phase space convergence, we apply the recently introduced approach of permutation reduction. Further, this method maps water molecules such that their resulting trajectories are restricted to a small region of space around a reference position without changing the physics of the ensemble. For density estimation, we adapted the efficient nearest neighbor (NN) method to the curved space of orientations. The NN method is entirely nonparametric and efficient on high-dimensional manifolds. For approximation of the total entropy, we apply the mutual-information expansion (MIE). The MIE is a systematic expansion of the entropy in mutual information terms by splitting the phase space into subsystems with reduce dimensionality.

Orientational entropies of water molecules are estimated by a the combination of these methods. Well-converged and spatially resolved many-body correlations of higher order are captured. The developed method was tested on specific distributions of orientations, the correlated orientations of water molecules from a pure water box, and the correlated orientations of water molecules around the small globular protein Crambin.

We found that orientational correlation is dominated by pair correlations between neighboring water molecules, and drops within the first two water shells. Further, the relative position of water molecules to each other plays an important role in three body-correlations, but their small mutual information suggests that higher order terms are not necessary to capture the orientational entropy of water.

3319-Pos Board B424

Charge Separation and Isolation in Water and Ice Particles on Strong Impacts

F. Wiederschein, E. Vöhringer-Martinez, A. Beinsen, R. Srama, S. Kempf, F. Postberg, B. Abel, H. Grubmüller.

Charge separation is a general phenomenon in nature. There has been vivid speculation and discussion about the mechanism of charge separation in condensed matter on strong impacts at small energies. Here we show that charge separation naturally occurs if water aggregates or particles with embedded charge carriers, e.g. ions, encounter a high energy impact even though no plasma occurs and the involved kinetic energies are much below any molecular ionization energy. We find that the charge distribution in the fragments resulting from a strong impact can simply be described by a three step model. The first level of the model is a simple statistical description of the resulting charge distribution at low salt concentrations by making usage of the Poisson distribution. The second step of describing the charge distribution of the dispersed fragments involves the mutual interaction between the charge particles in the condensed matter, which allows us to describe the charge process at higher salt concentrations. We achieved this by using implicit water Monte Carlo Simulation methods of the charged particles. Finally we included the full dynamics of the separation process into our model by using non-equilibrium Molecular Dynamics Simulations to describe the charge separation at high salt concentrations and high separation process velocities.

We present a microscopic model of the charging mechanism of fragments, that contributes to the understanding of a larger range of phenomena related to charges and charge separation in Nature. With this model we shed light on the charge mechanism of laser desorption experiments and discuss the impact of the current results for particle detection in space and possible implications for lightning formation in the atmosphere.

3320-Pos Board B425

Toward a Unified Model of Molecular Crowding: A Regression Approach to Predict Equilibria and Kinetics of Assembly Systems in Crowded Environments

Byoungkoo Lee, Philip R. LeDuc, Russell Schwartz.

Chemistry in living cells functions significantly differently from chemistry in a test tube. One defining characteristic of the intracellular environment is molecular crowding, which can dramatically alter the rates and equilibria of biochemical reactions, potentially either enhancing or inhibiting reactions depending on numerous physical parameters of a given system. However, it is extremely difficult to predict how crowding will quantitatively affect any particular reaction system or which physical factors of the system will be most critical. Sophisticated particle models provide a way to more accurately simulate chemistry in crowded systems, but at a computational cost that makes them infeasible for all but the most trivial reaction systems. With the goal of developing a unified model of molecular crowding, we developed a novel multi-scale approach to predict binding chemistry in crowded media using high-cost particle models of crowded conditions on simple test systems to train predictive regression models that can then be applied to low-cost differential equation or stochastic simulation models of more complicated systems. We show that a polynomial regression model can incorporate several interrelated parameters influencing chemistry under crowded conditions and accurately reproduce thermodynamic binding equilibria from stochastic off-lattice simulations of binding chemistry in crowded media. The model accurately reproduces the results of particle simulations over a broad range of variation of both independent and cross-dependent physical parameters expected to influence the crowding effect. We further show how the approach can be extended to efficiently capture the effects of molecular crowding on kinetic rate parameters. The work thus makes an important step toward the long-term goal of building computational models of reaction chemistry in the cellular environment that are both computationally tractable and predictive for large, complex systems.

3321-Pos Board B426

A Structurally Flexible Protein Backbone for the MARTINI Coarse Grained Force Field

Xavier Periole, Siewert-Jan Marrink, Peter Tieleman.

By reducing the level of description of a system as compared to atomistic models coarse grained (CG) molecular force fields allow simulating larger systems for longer time scales, thereby probing exciting properties of biological systems. It is our constant effort to improve their accuracy and range of applicability.

The MARTINI CG model defines a library of beads or super-atoms corresponding to chemical entities (defined by 3-6 non-H atoms) for which the interaction strengths are parameterized against thermodynamic (partitioning free energies) and structural data extracted from experiments and simulations. Virtually any molecular topology can be built from a combination of beads that reproduces structural and thermodynamic available data for that particular molecule. Molecular topologies are available for a large variety of molecules including lipids, amino acids and proteins, and sugars.

Here we present a refined version of the MARTINI force field for proteins in which restraining the secondary structure is not required anymore. This is achieved by restoring directionality in the backbone interactions. To do so a dipole (two net charges kept at a fix distance) is placed on the peptide bond of the backbone. We show that this simple representation coupled with a rigorous parameterization of the dipole and related bonded/non-bonded interactions is able to capture some essential mechanical and physicochemical properties of the polypeptide backbone. In particular the backbone may access both extended (β-sheet) and compact (α-helix) conformations using a single potential. A few simple test cases are shown to illustrate the structural flexibility of the new backbone and its ability to stabilize secondary structure elements in proteins. The potential is tested with both regular and polarizable MARTINI water models.